4

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,552	06/21/2001	Michael W. Leviten	R-67	5854

26619 7590 06/22/2005

JOHN E. BURKE
GREENBERG TRAURIG LLP
1200 17TH STREET, SUITE 2400
DENVER, CO 80202

EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,552	LEVITEN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1-7,9 and 11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10 and 17-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 3-28-05 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 18-25 have been added. Claims 1-25 are pending.

Election/Restrictions

This application contains claims 1-7, 9 and 11-16 drawn to an invention nonelected with traverse in the reply filed on 11-13-02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 8, 10 and 17-25 are under consideration.

Specification

The amendment filed 3-28-05 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The addition of the application numbers added to the paragraph starting on pg 10, line 5, is new matter. No support for the patent applications is found in the specification as originally filed. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 101

Claims 8, 10 and 17 remain rejected and claims 18-25 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility for reasons of record.

Claims 8 and 17-25 are directed toward a transgenic mouse comprising a null Cerberus (Cer1) allele.

The specification made the mice (pg 51, lines 1-6). Two homozygous mice were tested in an open field test (pg 51, lines 9-14; pg 52, Table 1). Applicants conclude that increased number of fecal boli during the ten-minute test indicated the mice had increase anxiety.

The mice claimed and described in the open field test study do not have a specific or substantial utility. It is not readily apparent that the results are statistically significant because only two knockout mice were tested. The results of the open field test merely indicate the mice defecated more frequently. It cannot be concluded that increased defecation is a sign of anxiety and not some muscular or gastrointestinal dysfunction. Significant "further experimentation" would be required to use the results of the open field test to determine the function of the cerberus gene. As such, mice with a disruption in the cerberus gene comprising SEQ ID NO:1 that defecate more frequently than a wild-type mouse in an open field test does not have utility as a model for anxiety.

The specification suggests using the mice as a model of disease, specifically as a model for neurological phenotypes (pg 17, line 30). The mice claimed do not have utility as a model of disease. The specification does not correlate any disease in humans to increased anxiety as claimed. The specification does not correlate

increased anxiety found in humans to a disruption in a cerberus gene. Therefore, using the mice as a model of disease is not a specific or substantial utility.

The specification suggests using the mice to identify agents that ameliorate a phenotype (pg 18, line 8). Using the mice to identify agents capable of altering a phenotype would require further research and is not a "substantial utility" or "specific utility" because the mouse may not be capable of identifying agents capable of treating disease. Bowery (Pharm. Rev., 2002, Vol. 54, pg 247-264) taught,

> "no unique pharmacological or functional properties have been assigned to either subunit or the variants" of $GABA_B$. "The emergence of high-affinity antagonists for $GABA_B$ receptors has enabled a synaptic role to be established. However, than antagonists have generally failed to establish the existence of pharmacologically distinct receptor types within the $GABA_B$ receptor class. The advent of $GABA_{B1}$ knockout mice has also failed to provide support for multiple receptor types" (pg 247, col. 2, line 4 on).

Thus, knockout mice may be used to identify agents that bind to the knocked out gene ($GABA_B$ in the case of Bowery or GPCR-like protein in the instant application), but the agent may not treat disease or ameliorate any symptom of disease. Further research would be required to determine how to use such an agent identified using the mouse, which is not a "substantial utility" (see Utility Guidelines for examples of things that do not have "substantial utility" "C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility"). Using the mice to identify agents capable of altering a

phenotype is also not a "specific utility" because the agent may be affecting other proteins in the pathway and not the cerberus protein itself. Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be found using wild-type mice. Furthermore, the specification does not identify any such agents using the mice. Therefore, using the mice to identify agents that alter the increased sensitivity to pain is not a specific, substantial or credible utility.

The specification suggests using the mice to identify agents that affect cerberus function (pg 18, lines 30-31). The mouse claimed couldn't be used to identify agents that act on cerberus because the mice do not express cerberus.

It was "well-known" in the scientific community at the time of filing to knock out a gene in a mouse in an attempt to determine its function; however, it was also "well-known" that the mouse may only provide clues to the function of the gene and that the mouse may not be capable of determining the function of the gene. While the mouse may have "scientific utility," "scientific utility" is not the same as "patentable utility" or a "well-established" utility.

The utility guidelines specifically state that further research is not a "substantial utility":

> [T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study of mice would have been required to determine how to use the mouse of applicants' invention (with decreased anxiety or increased pain threshold) as a model of disease. Further study would be required to determine the function of the disrupted gene. The overall phenotype of the applicants' mice does not correlate to any disorder; therefore, further study would be required to determine how to use the mice to study a disorder. Thus, using the mice claimed for further research is not a "substantial utility."

Using the mice to identify the function of the knocked out gene is not a "substantial utility" or "specific utility" because the phenotype may be caused by other proteins compensating for the deleted gene. Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). Thus, knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility"

because the phenotype may be a result of other compensating proteins and not the knocked out gene.

The function of a gene may not be found by studying a knockout mouse. Mombereau (Neuropsychopharmacology, 2004, Vol. 29, pg 1050-1062) used knockout mice that had increased anxiety further study to determine the function of $GABA_B$ receptor. Mombereau did not teach how to use mice with decreased anxiety as claimed. In addition, Mombereau did not determine the function of the $GABA_B$ receptor. Mombereau administered compounds known to antagonize $GABA_B$ receptor (found in *in vitro* assays, not in the mice) to the mice. Mombereau concluded that the mice merely confirmed $GABA_B$ was involved in a molecular pathway relevant for the manifestation of anxiety or depression. Mombereau did not determine the function of $GABA_B$ receptor using the $GABA_B$ -/- mice. Mombereau concludes "we acknowledge both the inherent difficulties and the caution needed in the interpretation of behavioral analysis of genetically modified mice such as the $GABA_B(1)$ -/- mice, which have overt behavioral disturbances, in more defined tests relevant to psychopathology. Nonetheless, the current data show that even such mice can still be utilized to give important indicators of the role of a given protein, in this case the $GABA_B$ receptor, in a molecular pathway relevant for the manifestation of anxiety or depression. These assertions can then be confirmed more parametrically using appropriate pharmacological activators and antagonists as we have done using novel $GABA_B$ receptor positive modulators and antagonists" (¶ bridging pg 1059-1060). Mombereau used the antagonists to confirm the "antidepressant-like phenotype of $GABA_B$ -/- mice pharmacologically (pg 1059, col.

1, 2nd full ¶, line 1-4). Therefore, using a mouse to merely obtain clues of the role of a protein in a molecular pathway of anxiety or to confirm the phenotype of the mouse pharmacologically as described by Mombereau is not a specific or substantial utility because it is generic to a pathway of anxiety and because it does not result in determining the function of the protein within the pathway.

Overall, the mice claimed do not have a "well-established utility" because using the mice for further research (to determine how to use the mouse as a model of non-disclosed disease, to determine the function of the gene or to identify agents capable of altering a phenotype) is not a "specific utility" or "substantial utility."

Claim 10, directed toward making a transgenic mouse, is included because the mouse being made does not have utility.

Applicants argue that one of skill would have recognized that the mouse has a well-established utility for defining the function and role of the disrupted gene, i.e. a tool in studying gene function (pg 8-11 of response filed 11-8-04). Applicants cite MPEP 2701 II(A)(3). Applicants cite an NIH report from 2004, Austin (Nature Genetics, 2004, Vol. 36, No. 9, pg 921-24), Genes VII (Lewin, Oxford University Press, 2000), Crawley (2000, What's wrong with my mouse, Behavioral phenotyping of transgenic and knockout mice, Wiley-Liss) and Crabbe (Science, 1999, Vol. 284, pg 1670-1672), which state knockout mice can be used to determine the function of genes. Applicants' arguments are not persuasive. MPEP 2701 II(A)(3) states:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible. (underlining added for emphasis)

First, the NIH report (2004), Austin (2004), and Molecular Biol. of the cell (2002) were not available at the time of filing and cannot be used to establish what was "well-established" at the time of filing.

Second, while the NIH report suggests knockout mice may be models of disease, one mouse with "decreased susceptibility to depression " (claim 17) is not a model of any disease. In fact, mice with decreased susceptibility to depression are the opposition of models of depression.

Lastly, the references merely suggest using knockout mice to study the function of targeted genes, which does not rise to the level of a substantial utility according to the utility guidelines. The NIH report states knockout mice can be used to elucidate gene function. Austin states null-reporter alleles should be created as a starting point for studying the function of every gene. The Molecular Biology of the Cell states mutant mice can be an invaluable tool for investigating gene function. Gene VII states knockout mice are used to investigate directly the importance and function of a gene. Joyner states gene targeting in ES is used to study gene function in a mammalian organism. Matise states knockout ES cells can be used to study gene function in cell culture and in vivo. Crawley states knockout mutations provide a means for understanding gene function. None of references teach the mice will determine the

function of the gene. Applicants have used the mice in phenotype analysis tests, but applicants have not determined the function of the gene. Simply using the mice for further research of the cerberus gene is not a specific or substantial utility. None of the references teach a specific or substantial utility for mice with a disruption in the cerberus gene as claimed.

In summary, the MPEP states a well-established utility must be specific, substantial and credible. In this case, using the mice to determine the function of the cerberus gene rises merely to the level of a scientific utility, but does not rise to the level of a specific, substantial and credible utility. Significant further research would be required to determine the function of the cerberus gene using only the expression analysis suggested by applicants or any of the phenotypic analysis exemplified on pg 51-52. One of skill would not gain any additional information of the role of the Cerberus gene by repeating the open field test and observing the mice walk slow and defecate. It would require one of skill undue effort to determine what experiments to do next to determine the role of Cerberus in an anxiety pathway because applicants have provided no further blaze marks to do so. The mice claimed do not compare to "gas chromatographs, screening assays and nucleotide sequencing techniques" because the mice do not necessarily reveal the function of the cerberus gene. Using the mice to determine where the protein is expressed is not a substantial or specific utility in this case because would not reveal the function of the cerberus gene. Therefore, using the mice to determine the function of the cerberus gene is not a well-established utility because the mice may not be capable of determining the function of the cerberus gene.

Applicants argue the mice have increased anxiety and therefore are useful for a particular purpose. Applicants' argument is not persuasive. The mice have "hypoactivity" which does not correlate to anxiety. Less than normal activity does not correlate to increased anxiety as asserted by applicants. Hypoactivity is a generic condition and may apply to depression, physical disabilities, motor skill abnormalities, etc. The mice with hypoactivity do not have a specific or substantial utility because the phenotype is not specific to a disease and does not necessarily indicate the cerberus gene is involved in an anxiety pathway.

Applicants argue Mombereau mice with increased anxiety were well-known in the art as useful tools in the discovery of anxiolytics. Applicants' argument is unfounded. Mombereau was not available at the time of filing and cannot be used to establish a well-established utility for mice with increased anxiety. Furthermore, Mombereau did not discover the anxiolytic using the mice. Lastly, Mombereau merely used mice having increased anxiety for further study but did not determine the function of $GABA_B$ receptor. The data merely suggested the $GABA_B$ receptor altered GABA(A) receptor function (abstract). Therefore, Mombereau does not support applicants' assertion that mice with increased anxiety were well-known tools for identifying agents that treat anxiety.

Applicants cite Lewejohann and Haller which are not evidence of utility because they were not available at the time of filing. Neither reference determined the function of the knockout gene using the knockout mouse. In the case of Lewejohann, the researches merely conclude that BC1 contributed to

the "aptive modulation of behaviour" [sic]. Lewejohann did not determine the function of BC1 or how BC1 modulated behaviour. The results were not specific to anxiety. In the case of Haller, antagonists of CB1 were required for the assays described by Haller. In the case of the instant invention, no modulators of cerberus were known at the time of filing. Significant further research would be required to isolate modulators of cerberus because the mice of applicants invention do not express cerberus and because compounds identified as altering a phenotype using the mice of applicants' invention may actually be modulating a protein in a pathway related to cerberus protein and not cerberus itself (see Olsen cited above who taught proteins in a pathway may compensate for the disrupted gene and cause the phenotype and that the phenotypes of mice with anxiety are generic to a pathway of proteins.

Applicants cite en re Brana and state the PTO has the initial burden of challenging the asserted utility in the disclosure (pg 14 of response). Applicants argue that contrary to the product in En re Brenner, whose sole 'utility' consisted of its potential role as an object of use-testing, the mouse claimed can be used to determine the function of SEQ ID NO:1. Applicants' arguments are not persuasive. *In re Schoenwald*, 22 USPQ2d 1671 (CA FC 1992) indicated that a product known in the art did not necessarily have patentable utility. The examiner has challenged all of the asserted utilities in the disclosure and has challenged what applicants consider "well-established" utilities. The mouse claimed might only provide a clue to a pathway in which SEQ ID NO:1 is

involved. This is not a specific utility because results from the tests only indicate SEQ ID NO:1 is involved in a pathway relating to anxiety. The phenotype provides only a clue that SEQ ID NO:1 is generically involved in a pathway having a number of proteins. Using the mouse to determine the function of SEQ ID NO:1 is not credible or substantial because the function of SEQ ID NO:1 may never be found using the mouse. Assuming further study of the mouse will elucidate the function of SEQ ID NO:1, the amount of research required to do so would be significant. The specification does not guide those of skill in any particular direction so that one of skill could simply perform an assay to determine the function of SEQ ID NO:1.

Applicants cite Doetschman (Lab. Animal Sci. 1999, Vol. 49, pg 137-143), which taught knockout phenotypes provide accurate information concerning gene function (pg 16 of response). Applicants' argument is not persuasive. Doetschman taught that the phenotype may be caused by the mixed background of the knockout mice and not be caused by the knockout (¶ bridging pg 140-141). Doetschman does not teach that every mouse with a disruption will reveal the function of the disrupted gene. The knockout mice described by Doetschman merely provide clues as to the disrupted gene's function. Significant further investigation would be required to determine the function of a gene using any mouse described by Doetschman. Therefore, Doetschman does not establish that any mouse with a disruption in any gene has a "well-established" utility.

Applicants are reminded that In re Schoenwald, 22 USPQ2d 1671 (CA FC 1992) indicated that a product known in the art did not necessarily have patentable utility. In this case, the mouse claimed might only provide a clue to a pathway in which SEQ ID NO:1 is involved. This is not a specific utility because results from the tests may only indicate SEQ ID NO:1 is involved in a pathway. Increased sensitivity to pain provides only a clue that SEQ ID NO:1 is generically involved in a pathway influenced by numerous proteins. Assuming further study of the mouse will elucidate the function of SEQ ID NO:1, the amount of research required to do so would be significant. The specification does not guide those of skill to any particular blaze marks so that one of skill would know the assays required to determine the function of SEQ ID NO:1.

Applicants argue the mouse has specific utility because only the Cerberus gene is disrupted. Applicants' argument is not persuasive. The disruption is not specific to the Cerberus gene because other genes may be affected by the targeting construct. Scarff (genesis, 2003, Vol. 36, pg 149-157) taught the phenotype of knockout mice may be a result of the retention of the selectable marker gene in the mice, which affects expression of neighboring genes, i.e. the observed phenotype may not be a result of the disruption of the gene itself.

> It is becoming apparent that retention of the selectable marker gene in knockout mice can lead to a confounding phenotype. In most cases the retained selectable marker gene affects the expression of neighbouring genes."
> (pg 155, col. 1, 2nd full ¶).

Scarff cites Fiering (Gene Dev., 1995, Vol. 9, pg 2203-2213); Hug (Mol. Cell Biol. 1996, Vol. 16, pg 2906-2912); Pham (PNAS, 1996, Vol. 93, pg 13090-13095); Leder (Blood,

1997, Vol. 90, pg 1275-1282); DeJarnette (PNAS, 1998, Vol. 95, pg 14909-14914; and Ren (Dev. Dyn., 2002, Vol. 225, pg 305-315). Without evidence to the contrary, any abnormal phenotype observed in the mice described by applicants is not specific to the disruption in the gene itself because it may be a result of the selectable marker gene affecting neighboring genes. Therefore, the mice claimed do not have a utility that is specific to the Cerberus gene disruption.

Applicants' argument bridging pg 17-18 of the response is unclear. The examiner's position is that the mice may never reveal the function of the Cerberus gene. The specification does not provide the blaze marks for one of skill to determine the assays that will reveal the function of the gene.

Applicants' argument in the 1st full ¶ of pg 18 is unclear. Applicants assert the issue of additional research relates to enablement and not utility. Applicants' argument is moot. Further research would be required to use the mouse to determine the function of the Cerberus gene. The examiner has merely provided reasons why the specification does not provide the blaze marks for one of skill to determine the assays required to do so. This is appropriate under utility and also applies to enablement.

Claim Rejections - 35 USC § 112

Enablement

Claims 8, 10 and 17 remain rejected and claims 18-25 are rejected under 35 U.S.C. 112, first paragraph for reasons of record. The claimed invention is not supported by either a specific or substantial asserted utility or a well established utility

for the reasons set forth above; therefore, one skilled in the art clearly would not know how to use mice having a disruption in SEQ ID NO:1 as claimed.

Applicants' arguments to the enablement rejection are found in the arguments to the utility rejection, which have been addressed above in the utility rejection.

New Matter

Claims 8, 10 and 17-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "null allele" (claim 8) is new matter because the phrase does not have support in the specification as originally filed. Null allele is defined as "an allele whose effect is either an absence of normal gene product at the molecular level or an absence of normal function at the phenotypic level (Genetics Glossary definition of "null allele). In the paragraph bridging pg 6-7, applicants describe "disruption;" however, the scope of "disruptions" is not the same as the scope of "null allele". Therefore, it is not readily apparent that applicants had originally contemplated the scope of "null allele" as now claimed. 6,080,910 defined "null alleles" as an allele incapable of expressing a functional protein; null alleles may be generated by deleting a portion of the coding region, deleting the entire gene, introducing an insertion and/or a frameshift mutation, etc. or may be used to introduce a modification (e.g. one or more point mutations) into a gene (col. 10, liens 17-21). The scope "null alleles" in '910 is different than the scope of

disruptions on pg 6-7. It is not readily apparent that applicants contemplated the scope of "null alleles" defined in by Genetics Glossary or US Application '910.

Indefiniteness

Claims 8, 10 and 17-25 are rejected and new claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of a "null Cerberus allele" in claim 8 as newly amended are indefinite. It is unclear if the phrase is limited to a mouse without any of the cerberus gene, or if the phrase encompasses a mouse without any of the coding region of the cerberus gene, or a mouse with a disruption in the cerberus gene, wherein said disruption does not allow production of functional cerberus protein, or a mouse with a disruption in the cerberus gene, wherein said disruption causes less than normal amounts of functional cerberus protein. "Null allele" can be defined as "an allele whose effect is either an absence of normal gene product at the molecular level or an absence of normal function at the phenotypic level (Genetics Glossary definition of "null allele). US Application 6,080,910 defines "null allele," but the definition does not have the same scope as the Genetics Glossary definition of "null alleles or as the "disruptions" described in the paragraph bridging pg 6-7. Furthermore, the definition in '910 was not available at the time of filing. Therefore, the metes and bounds of structures encompassed by such alleles cannot be determined.

Claim 10 remains indefinite because a "pseudopregnant mouse" does not give birth as claimed.

The rejection regarding "anti-depressive" in claim 17 has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 8, 10 and 17-24 are rejected under 35 U.S.C. 102(a) as being anticipated by Stanley (Genesis, 2000, 26: 259-264).

Stanley taught a transgenic mouse comprising a heterozygous or homozygous disruption the in the cerberus gene. Stanley produced the transgenic mouse by introducing a targeting construct comprising nucleotide sequences homologous to regions of exon I of the cerberus gene, a hygromycin resistance gene and a gene encoding LacZ into a mouse ES cell, transferring the ES cell into a mouse blastocyst to create a transgenic embryo, and implanting the blastocyst into a recipient female, wherein the embryo was allowed to develop to term. The heterozygous mouse was then bred to homozygosity (see "Methods" section (pg 261-262) and 1st ¶, under Results, pg 260). The mice taught by Stanley inherently have "decreased susceptibility to depression" (17) and "increased anxiety" (20) as claimed because the mice of

Stanley have the same disruption as the mice described by applicants. Without evidence to the contrary, the mouse Cer1 gene disrupted by Stanley inherently is the Cre1 allele claimed and encodes SEQ ID NO:1 and 2 (claims 21 and 22).

Claim Rejections - 35 USC § 103

Claims 8, 10 and 17-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Conquet (Neuropharm. 1995, Vol.34, No. 8, pg 865-870) in view of Mara (GenBank Accession No: AA120122, Nov. 21, 1996).

Conquet made a mouse with a heterozygous and homozygous disruption in a gene by inserting LacZ and neo genes into the gene (¶ bridging pg 865-866; pg 886, Fig. 1A; pg 868, Fig. 3 and col. 1, line 6-8 and 17-20). Conquet did not disrupt SEQ ID NO:1.

However, Marra taught SEQ ID NO:1.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to disrupt a gene in a mouse as taught by Conquet, wherein the gene was SEQ ID NO:1 as taught by Marra. One of ordinary skill in the art at the time the invention was made would have been motivated to specifically disrupt SEQ ID NO:1 instead of the glutamate receptor gene described by Conquet to gain clues to the function of SEQ ID NO:1 in vivo. One of ordinary skill would have had a reasonable expectation of successfully making a mouse based on the combined references because GenBank Accession No. AA914066 provided a coding sequence (mRNA or cDNA) that could easily be used to make homology arms capable of recombining with

the Cerberus gene. While Conquet had knowledge of the genomic sequence, the genomic sequence was not essential to making the targeting construct used to make the mouse. Applicants' disclosure provides no description of how to use mRNA to make a knockout construct greater than the combined teachings of Conquet and Marra.

The mice taught by the combined teachings of Conquet and Marra inherently have "decreased susceptibility to depression" (17) and "increased anxiety" (20) as claimed because the mice both have a disruption in SEQ ID NO:1.

Thus, Applicants' claimed invention as a whole is prima facie obvious in the absence of evidence to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER